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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,461	12/04/2003	John D. Shaughnessy	D6485	6235

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,461	SHAUGHNESSY, JOHN D.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to the Amendment

The Amendment filed on 12/04/2006 in response to the previous Non-Final Office Action (09/14/2006) is acknowledged and has been entered.

Claims 15 and 18-19 are currently pending and under consideration.

The Declaration under 37 CFR 1.132 filed on December 4, 2006 by the inventor, Dr. Shaughnessy, is insufficient to overcome the rejection of claims 15 and 18 under 35 U.S.C. 112, first paragraph, enablement, as set forth in the last Office action because the Declaration does not appear to be commensurate in scope with the claimed invention. In particular, the Declaration sets forth the effects of neutralizing antibody against DKK1 on bone mineral density in preclinical nonmyelomatous SCID-rat model, wherein treatment with DKK1 antibody resulted in a significant increase in bone mineral density of nonmyelomatous implanted bone relative to uninvolved mouse femurs from myelomatous hosts which did not change. However, it is unclear how this data equates back to the instant claims which are drawn to a method of diagnosing a DKK-1 lytic bone disease in any individual comprising measuring the expression level of DKK1 protein.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 15 and 18 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing a Dkk-1 associated lytic bone disease in an individual having multiple myeloma, comprising examining the expression level of the human homologue of Dickkopf-1 (DKK-1) protein, does not reasonably provide enablement for a method of diagnosing any and/or all Wnt antagonist-associated lytic bone diseases in any test individual, comprising examining the expression level of the human homologue of Dickkopf-1 (DKK-1) protein in said test individual. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed

invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of diagnosing a Wnt antagonist-associated lytic bone diseases in a test individual, comprising examining the expression level of the human homologue of Dickkopf-1 (DKK-1) protein in said test individual. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of diagnosing a Wnt antagonist-associated lytic bone diseases in a test individual, comprising examining the expression level of the human homologue of Dickkopf-1 (DKK-1) protein in said test individual. Thus, the claims encompass diagnosing any and/or all Wnt antagonist –associated lytic bone disease in any individual based on the increased expression of Dickkopf-1 (DKK-1) protein.

Guidance in the specification and Working Examples

The specification teaches (page 19, lines 13-20) that examples of secreted antagonists of WNT such as Frizzled (Fz)-related proteins (FRPs), Cerberus, Wnt inhibitor factory (WIF) and Dickkopf (DKK). The specification further teaches that 174 patients with "newly" diagnosed multiple myeloma, 16 patients with monoclonal gammopathy of undetermined significance, 9 with Waldenstroms macroglobulinemia, and 45 normal persons were studied in the present invention (page 27, lines 10-16). Specifically, the specification provides (page 35, Example 8) an analysis of the results obtained from 173 patients with myeloma, wherein the DKK1 signal for patients with 1 + MRI and no x-ray lesion differ significantly compared to patients with no MRI and no x-ray lesions, but does not differ significantly compared to patients with 1 + MRI and 1 + x-ray. Moreover, the specification teaches (page 9, Example 9) a correlation between global gene expression of DKK-1

and lytic bone lesions in multiple myeloma. Thus, while the specification clearly teaches a diagnosis of bone disease in a multiple myeloma patient comprising comparing the level of DKK-1 expression in an individual with multiple myeloma compared to a "normal" individual, the specification appears to be silent on a correlation between DKK-1 expression and any and/or all Wnt antagonist-associated lytic bone diseases in any and/or all individuals. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the diagnosis of a bone disease, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of diagnosis is extremely large given the unpredictability associated with correlating the level of DKK-1 protein expression level with the ability to provide a diagnostic evaluation of a patient suspected of exhibiting a lytic bone disorder.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that one activity associated with the DKK family of proteins is the modulation, e.g., antagonism, of the activity of the Wnt family of secreted proteins. For example, McCarthy (WO 00/52047, 2000, of record), teach a method of diagnosing a disease or disorder associated with aberrant expression or activity of DKK (abstract). While McCarthy contemplates determining the risk of developing a disease associated with aberrant expression or activity of a DKK protein (page 96, lines 14-16), there does not appear to be any demonstration that the DKK family of proteins can be used to diagnose a WNT associated lytic bone disease in any and/or all individuals.

In the instant case, the specification provides neither guidance on nor exemplification of how to correlate the level of DKK-1 protein expression level with the ability to provide a diagnostic evaluation of a patient suspected of exhibiting a lytic bone disorder. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for cancer detection, the basic principles taught are clearly applicable to other disorders such as lytic

bone diseases. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In addition, Slamon et al. (Science Vol. 235, January 1987, pages 177-182) teach other essential factors that are known to be important in the prognosis of breast cancer in individual patients such as size of the primary tumor, stage of the disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes involved with disease (page 178, 1st column, 2nd paragraph). Such data are critical to assessing actuarial curves for relapse (Figure 3), and for comparing disease-free survival and overall survival to prognostic factors (Table 4).

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

In response to this rejection, Applicants submit that the instant specification teaches the importance of Wnt signaling pathway in bone development, wherein the Wnt family of secreted growth factors initiate signaling via the Frizzled (Fz) receptor and its co-receptors, LDL receptor-related protein 5 or 6 (LRP5 or LRP6) and that DKK1 specifically inhibits Wnt signaling by binding to LRP5/LRP6 component of the receptor complex (pages 19, 20, 21 and 22). In particular, Applicants assert that the increase in WNT signaling mediated by decrease in DKK-1 inhibition results in higher osteoblast activity leading to high bone mass and provides evidence for inhibition of DKK1 as a target for the prevention or treatment of osteoporosis. Moreover, Applicants contend that the specification teaches that the expression of two secreted Wnt signaling antagonist, SFRP-3/FRZP and DKK-1 in multiple myeloma patients was linked with the development of lytic bone lesions (Examples 8 and 9). Applicants further submit that Example 17 provides important information on the role of DKK-1 in osteoblast differentiation. Specifically, Applicants assert that alkaline phosphatase, a specific marker of osteoblast differentiation was inhibited in C2C12 cells cultured with BMP-2 and bone marrow serum with a DKK-1 concentration >12 ng/mL (from donors with multiple myeloma), whereas a reversal of alkaline phosphatase inhibition was observed in the presence of anti-DKK-1 antibody. Thus, Applicants contend that this clearly demonstrates the inhibitory effect of DKK-1 on osteoblast activity. Furthermore, Applicants submit that a Declaration by the inventor, Dr. John Shaughnessy, unquestionably supports the critical role of DKK1 in bone remodeling in adults. In particular, Applicants contend that the Declaration clearly demonstrates that the application of a neutralizing antibody directed to DKK1 results in an increase in bone mineral density of non-myelomatous bones, in vivo.

These arguments have been carefully considered, but are not found persuasive.

Pertaining to Applicants arguments with respect to the Wnt signaling pathway, the Examiner acknowledges and concedes that the Wnt signaling pathway is important in bone development; and further, that DDK1 is a component of this pathway. However, the Examiner recognizes that the instant claims are not drawn to determining the role of DKK1 in the Wnt-signalling pathway which is taught in the specification, but encompass DKK1 as a marker for a lytic bone disease in any individual, wherein an increased expression is indicative a lytic bone disease. In this instant case, the specification appears to have only linked increased DKK-1 protein expression in multiple myeloma patients with lytic bone lesions (Examples 8 and 9). As such, Applicants arguments with respect to

inhibition of DKK-1 with an anti-DKK-1 antibody do not appear to be commensurate in scope with the claimed invention because inhibition of DKK-1 with an anti-DKK-1 antibody does not appear to suggest a nexus between increased expression of DKK-1 and diagnosis of a lytic bone disease. Regarding the Declaration by the inventor, Dr. Shaughnessy, the Examiner recognizes that the Declaration does not appear to be commensurate in scope with the claimed invention. In particular, the Declaration sets forth the effects of neutralizing antibody against DKK1 on bone mineral density in preclinical nonmyelomatous SCID-rat model, wherein treatment with DKK1 antibody resulted in a significant increase in bone mineral density of nonmyelomatous implanted bone relative to uninvolved mouse femurs from myelomatous hosts which did not change. However, it is unclear how this data equates back to the instant claims which are drawn to a method of diagnosing a DKK-1 lytic bone disease in any individual comprising measuring the expression level of DKK1 protein.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 15 and 18-19 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 11/176,739 (erroneously 10/176,739 in the previous office action).

Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus. The genus method of determining the potential of developing bond disease in a multiple myeloma patient by examining the expression level of a WNT signaling antagonist claimed in the conflicting patent application appears to fall within the same scope as the species method of diagnosing a Wnt antagonist-associated lytic bone disease in a patient comprising examining the expression level of the human homologue of Dickkopf-1 (DKK-1) protein claimed in the application being examined.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

(Note in the previous Office Action, the Examiner erroneously made the ODP rejection over copending Application 10/176,739, but realized latter that it should have been 11/176,739. The Examiner apologizes for this mistake.)

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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